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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,200	11/08/2006	Rudolf Moser	EPROV-0024	4126

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EXAMINER	
STONE, CHRISTOPHER R	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
09/18/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mwzb.com

Office Action Summary	Application No.	Applicant(s)	
	10/562,200	MOSER ET AL.	
	Examiner	Art Unit	
	CHRISTOPHER R. STONE	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 19-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed June 5, 2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Status of Claims

Claims 1-24 are currently pending. Claim 18 is withdrawn from further consideration as being drawn to a nonelected invention. Claims 1-17 and 19-24 are currently under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-16 and 19-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Odin et al in view of Beggs et al (US 5,434,087) and Nijkerk et al (WO 95/26963). (All documents listed on PTO 1449, filed November 8, 2006)

Claims 1, 2, 4-16 and 19-24 are drawn to a pharmaceutical composition comprising 5,10-methylenetetrahydrofolic acid and citrate at a pH of 7.5 to 10.5.

Odin et al teaches a composition comprising the calcium salt of 5,10-(6R,S)-methylenetetrahydrofolic acid (CH_2FH_4) and optionally vitamin C (ascorbic acid, a reducing agent) at a pH of 8.95, prepared with and without the exclusion of atmospheric oxygen (p. 448, 2nd column, 3rd paragraph and p. 451, 1st column, 4th paragraph) useful in the biomodulation of 5-fluorouracil (5-FU) in the treatment of cancer (p. 454, 2nd column, 2nd paragraph). Odin does not teach the composition further comprising citrate.

Beggs et al (US 5,434,087) teaches that citrate improves the stability of the reduced folic acid derivative 5-methyl-tetrahydrofolic acid (column 8, lines 31-35). Nijkerk et al (WO 95/26963) teaches that citrate is used as a stabilizer in pharmaceutical compositions and improves the stability of the reduced folic acid derivative, folinic acid (p. 1, line 37 to p. 2 line 4).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of the instantly claimed invention to add citrate to the composition of Odin et al and to prepare the composition (or stabilize the composition of CH_2FH_4) by

bringing the components together (i.e. treating the CH_2FH_4 with citrate) and adjusting the pH to 8.95, since citrate was known to improve the stability of reduced folate derivatives, thus resulting in the practice of the instantly claimed invention with a reasonable expectation of success. As for claim 19, Odin further teaches that the stability of CH_2FH_4 is improved in more alkaline solutions (p. 453, right column, 2nd full paragraph), providing the motivation for one of ordinary skill in the art to increase the pH to greater than 8.5, thus resulting in the instantly claimed composition with a reasonable expectation of success. Odin further teaches that tetrahydrofolic acid (FH_4) is useful for the biomodulation of 5-fluorouracil (5-FU) in the treatment of cancer (p. 454, 2nd column, 2nd paragraph). Therefore it would have been obvious to one of ordinary skill in the art at the time of the instantly claimed invention to add FH_4 and/or 5-FU to the composition mentioned above, since FH_4 and the composition were known to be used for the same purpose and 5-FU and the composition where known to be useful when administered together. Applicant is reminded of in re Kerkhoven, which affirmed that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) Additionally, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to formulate the composition into a lyophilization solution and a lyophilate, since lyophilization is commonly used in the art to preserve pharmaceuticals.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Odin et al, Beggs et al (US 5,434,087) and Nijkerk et al (WO 95/26963) as applied to claims 1, 2, 4-16 and 19-24 above, further in view of Cobb et al (US Patent 5989566).

Claim 3 is drawn to a pharmaceutical composition comprising 5,10-methylenetetrahydrofolic acid, citrate and formaldehyde at a pH of 7.5 to 10.5.

Odin et al, Beggs et al and Nijkerk et al as combined supra teach the aforementioned composition, but do not teach the composition further comprising formaldehyde.

Cobb et al teaches that formaldehyde is used as a preservative in pharmaceutical formulations (column 6, lines 1-3). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of the instantly claimed invention to add formaldehyde to the composition of 5,10-methylenetetrahydrofolic acid and citrate to preserve the components of the composition, thus resulting in the practice of the instantly claimed invention with a reasonable expectation of success.

In response to applicant's argument that the formaldehyde in the instantly claimed composition provides additional benefits other than the preservative activity taught by Cobb et al, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Odin et al in view of Beggs et al (US 5,434,087) and Nijkerk et al (WO 95/26963) as applied to claims 1, 2, 4-16 and 19-24 above, further in view of Rabelink et al (US PGPUB 2002/0052374) and Binderup (US PGPUB 2002/0183277).

Claim 17 is drawn to a pharmaceutical composition comprising 5,10-methylenetetrahydrofolic acid, citrate and capecitabine at a pH of 7.5 to 10.5.

Odin et al, Beggs et al and Nijkerk et al as combined supra teach the aforementioned composition, but do not teach the composition further comprising capecitabine.

Rabelink teaches that tetrahydrofolates are useful for increasing the therapeutic effects of fluorinated pyrimidines (paragraph [0002]). Binderup teaches that capecitabine is a fluorinated pyrimidine (paragraph [0032]).

Therefore it would have been prima facie obvious at the time the invention was made to add capecitabine to the composition of Odin et al, Beggs et al and Nijkerk, to potentiate the therapeutic effect of the drug, thus resulting in the practice of the instantly claimed invention with a reasonable expectation off success.

Response to Arguments

Applicant's arguments with regard to the rejections under 35 U.S.C. 112 are moot, since the rejections have been obviated by amendment. Applicant argues that the secondary references do not provide a reason to one of ordinary skill in the art to use citrate in the composition of Odin et al, since citrate would not have been expected to

increase the stability of the composition. This is found unpersuasive because although Beggs et al teaches that 5-methyl-tetrahydrofolic acid is unstable in solution, this does not negate the teaching that the 5-methyl-tetrahydrofolic acid is traditionally stabilized in solution with citrate (see e.g. column 3, lines 8-17 and column 8, lines 31-35) or the teaching that citrate additionally stabilizes another reduced folate (PGA or folic acid, column 8, lines 57-59), providing motivation to add citrate to the reduced folate solution of Odin et al. The art as a whole provides motivation to add citrate to reduced folate solutions in order to stabilize the solutions and thus it is not unexpected that citrate would stabilize the instantly claimed composition. With regards to the alleged unexpected synergistic results of increased stability relative to the composition of Odin, even if it were unexpected that citrate improves the stability of the instantly claimed composition (it is not for the reasons noted above), none of the examples adequately control for each of the following: temperature, pH and concentration of the solutions, so no meaningful comparison can be made. That is, the examples do not allow a direct comparison of the solutions at identical temperature, pH and concentration (each of which effects the stability of a particular compound in solution) to demonstrate citrate has a positive effect on the stability of the 5,10-methylenetetrahydrofolic acid solutions.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTOPHER R. STONE whose telephone number is (571)270-3494. The examiner can normally be reached on Monday-Thursday, 7:30am-4:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CRS

/Patricia A. Duffy/
Primary Examiner, Art Unit 1645